REMARKS

Status of the Claims

Claims 73, 78, 81-86, 88-98 and 100 were pending in the subject application. By this Amendment, Applicants have deleted claims 73, 78, 81-86, 88-90, 92, 95-96, and 100, without prejudice to Applicants right to pursue the subject matter of these claims in a future continuation or divisional application. Claim 93 was amended in order to limit the claimed subject matter to pro-NGF, sortilin receptor, an antibody which binds to an extracellular part of the sortilin receptor, and increased motor neuron survival, as suggested by the Examiner. The aforementioned claim limitations are made without prejudice, and Applicants maintain their right to pursue additional species (*e.g.* species of pro-neurotrophin, receptor, and receptor inhibitory agents) in future continuation or divisional application.

Support for amendments to claim 93 may be may be found inter alia in the specification, *e.g.*, at page 25, line 26; page 32, lines 7-10; page 32, line 29; page 27, lines 26 and lines 33-34; page 25, line 4; page 25, lines 18-19; and in the previous claims 78 and 100.

Applicants maintain that the amendments to claim 93 raise no issue of new matter and respectfully request that the amendment be entered. Accordingly, upon entry of this Amendment, claims 91, 93, 94, 97 and 98 will be pending and under examination.

Applicants respectfully request entry of these amendments in accordance with 37 C.F.R. 1.114 (Request for Continued Examination (RCE) practice), which RCE is also filed herewith.

Claim rejections

In the Office Action, the Examiner maintains rejections of claims 73, 78, 81-86, 88-98 and 100 under 35 U.S.C. 112, first paragraph for reasons related to scope of enablement. The

Examiner concludes that one of ordinary skill in the art would not know how to use the invention commensurate in scope with the claims which are drawn to providing treatment for any injury or dysfunction of the CNS or PNS, whereas the Declaratory evidence provides an effect of increasing survival of neurons, however the method is not descriptive of an inhibitory antibody in an animal suffering from any injury or dysfunction of the CNS or PNS as required by the claims.

Applicant thanks Examiner MacFarlane for granting the after-Final interview with Applicants' undersigned agent, Mary Johnson. In an effort to advance the prosecution of the present application, Applicants have amended claim 93 to further define the subject matter to pro-NGF (as the pro-neurotrophin), sortilin (as the receptor), and an antibody which binds to an extracellular part of the sortilin receptor (as the inhibitory agent). The claim is further limited to the scope of increased neuronal survival, whereas the Declaratory evidence of Dr. Eero Castrén submitted on June 15, 2009 provides a nexus for inhibiting the binding of pro-NGF to a sortilin receptor and increasing survival of neurons. The Declaratory evidence submitted on June 15, 2009 also provides an antibody which binds to an extracellular part of the sortilin receptor. Applicant believes that the present amendments to the claims and the prior Declaratory evidence place the application in condition for allowance. Such allowance is earnestly solicited.

During the February 23, 2010 telephone discussion with the Examiner concerning the prior Declaratory evidence, it was clarified that the inhibitory rabbit anti-sortilin IgG antibody provided with such evidence (see paragraph 18 and Appendix B of the Declaration of Dr. Eero Castrén) was first referenced in a publication by C. Munck-Petersen, et al. EMBO, 18(3):595-604 (1999). In order to provide further clarity, the soluble luminal domain (N-terminus) of the sortilin receptor was purified and used for generation of an anti-sortilin antibody, and the IgG fraction was purified from rabbit serum, as described in Munck-Petersen et al (1999) (see page 602, column 2, under the heading *RAP, antibodies and*

Western blotting).

Another example of an anti-sortilin antibody, particularly an anti-sortilin antibody binding to the extracellular domain (N-terminus) of the sortilin receptor, was provided in Munck-Petersen et al (1999). Applicant points to Munck-Petersen et al, 1999, page 602, column 2, under *RAP, antibodies and Western blotting,* wherein an antibody generated from the sortilin propeptide (amino acid residues P15-R28) is described and provides another example of an antibody directed against, and binding to, an extracellular part of the sortilin receptor.

In a paper by Nielsen et al, Journal of Biological Chemistry, 274(13):8832-36 (1999), both the rabbit anti-sortilin IgG antibody and the rabbit antiserum to the P15-R28 amino acid propeptide are referenced at page 8833, column 1, under the heading *Antibodies.*

Further examples of anti-sortilin antibodies, particularly anti-sortilin antibodies binding to the extracellular part of the sortilin receptor, were provided in the art at the time of filing the subject application, such as in Petersen, et al. Journal of Biological Chemistry, 272(6):3599-3605 (1997). Petersen, et al. (1997) describe a rabbit anti-(gp95/)sortilin antiserum generated from an N-terminal peptide sequence of the sortilin receptor corresponding to extracellular part of the sortilin receptor (See Petersen, et al. (1997) at Figure 4, and page 3600, column 2, in the paragraph under the heading *Transient Expression and Immunocytochemistry.*)

Also Nykjaer et al., Nature, 427:843-848 (2004) describe a mouse anti-sortilin antibody (anti-NTR3, Catalog No. 612101) produced by Transduction Biolabs (now BD Transduction Labs). (See Nykjaer, et al. (2004), at page 848, column 2, last paragraph, under the heading, *Induction of apoptosis in various cells.*) Although the Nature paper by Nykjaer was published in 2004, it was received 3 November 2003 and accepted 23 December 2003 (see

page 848). A copy of the Technical Data Sheet for the antibody of Catalog No. 612101, which is still available for purchase, is attached herewith and identifies that the immunogen (epitope to which the antibody binds) is in the extracellular part of the sortilin receptor.

The above-mentioned articles, Munck-Petersen et al (1999), Nielsen et al (1999), Petersen, et al. (1997) and Nykjaer et al. (2004), were each previously cited to the Examiner in an Information Disclosure Statement. An additional reference, Lin et al., Journal of Biological Chemistry, 272(39):24145-47 (1997) is provided as an example of a rabbit anti-rat sortilin antibody, generated from a peptide in the extracellular part of the rat sortilin receptor ("Peptide 2", amino acid residues N423-K438). (See Lin et al.(1997) on page 24146, column 1, under the heading *Gel Electrophoresis and Immunoblotting* and Figure 1.) The Lin et al. (1997) reference is filed in an Information Disclosure Statement herewith.

This information is provided as requested by the Examiner in order to illustrate the state of the art with regard to anti-sortilin antibodies at the time of filing the subject application.

Conclusion

For the forgoing reasons, Applicants believe that the application is now in condition for allowance. Such allowance is earnestly solicited.

If a further telephone interview would be of assistance in advancing prosecution of the present application, the Examiner is invited to telephone the undersigned at the number provided below.

No fee, other than the fee for the concurrently filed RCE, is deemed necessary in connection with the filing of this Amendment. However, authorization is hereby given to charge any underpayment, or credit any overpayment, to Deposit Account No. 50-3201.

Respectfully submitted,

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Technical Data Sheet

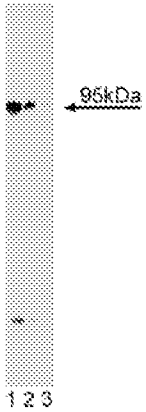
Purified Mouse Anti-Neurotensin Receptor 3

Product Information

Material Number:	**612101**
Alternate Name:	NTR3
Size:	150 µg
Concentration:	250 µg/ml
Clone:	48/Neurotensin Receptor 3
Immunogen:	Human Neurotensin Receptor 3 aa. 300-422
Isotype:	Mouse IgG1
Reactivity:	QC Testing: Human Tested in Development: Mouse, Rat, Dog, Chicken
Target MW:	95 kDa
Storage Buffer:	Aqueous buffered solution containing BSA, glycerol, and ≤0.09% sodium azide.

Description

Neurotensin (NT) is a neuropeptide that modulates dopaminergic transmission, triggers analgesic responses, induces hypotension, decreases gastric acid secretion, and activates lipid digestion. NT is a ligand for NT receptors, which include both G-protein coupled and non-G-protein coupled receptors. Neurotensin Receptor 3 (NTR3) is a non-G-protein coupled receptor that has a lumenal domain homologous to sorting proteins, and a short cytoplasmic tail homologous to mannose-6-phosphate/IGF-II receptor. NTR3 was also identified as sortilin/gp95, a component of GLUT4 vesicles in adipocytes that has been implicated in lipoprotein lipase degradation. NTR3 mRNA is expressed in brain, skeletal muscle, heart, and adipocytes. NTR3 mature protein has 44 N-terminal amino acid residues cleaved off, which may facilitate ligand binding to the receptor. Cellular localization of NTR3 is in the Golgi compartment and vesicles, as well as on the cell surface. In addition to roles in neuropeptide and lipoprotein degradation, NTR3 may also be involved in receptor protein sorting. Thus, NTR3 is a multifunctional transmembrane protein that acts as both a intracellular sorting receptor and extracellular ligand-binding receptor.



Western blot analysis of Neurotensin Receptor 3 on a PFSK-1 cell lysate (Human neuroectodermal tumor line; ATCC CRL-2060). *Lane 1: 1:250, lane 2: 1:500, lane 3: 1:1000 dilution of the mouse anti-Neurotensin Receptor 3 antibody.*

Preparation and Storage

The monoclonal antibody was purified from tissue culture supernatant or ascites by affinity chromatography.
Store undiluted at -20°C.

Application Notes

Application

Western blot	Routinely Tested
Immunofluorescence	Not Recommended

BD Biosciences
bdbiosciences.com

United States	Canada	Europe	Japan	Asia Pacific	Latin America/Caribbean
877.232.8995	888.259.0187	32.53.720.550	0120.8555.90	65.6861.0633	55.11.5185.9995

For country-specific contact information, visit bdbiosciences.com/how_to_order/

Recommended Assay Procedure:

Western blot: Please refer to http://www.bdbiosciences.com/pharmingen/protocols/Western_Blotting.shtml

Suggested Companion Products

Catalog Number	Name	Size	Clone
611942	PFSK-1 Cell Lysate	500 µg	(none)
554002	HRP Goat Anti-Mouse Ig	1.0 ml	(none)

Product Notices

1. Since applications vary, each investigator should titrate the reagent to obtain optimal results.
2. Please refer to www.bdbiosciences.com/pharmingen/protocols for technical protocols.
3. Caution: Sodium azide yields highly toxic hydrazoic acid under acidic conditions. Dilute azide compounds in running water before discarding to avoid accumulation of potentially explosive deposits in plumbing.
4. Source of all serum proteins is from USDA inspected abattoirs located in the United States.

References

Mazella J, Zsurger N, Navarro V. The 100-kDa neurotensin receptor is gp95/sortilin, a non-G-protein-coupled receptor. *J Biol Chem*. 1998; 273(41):26273-26276. (Biology)

Morris NJ, Ross SA, Lane WS. Sortilin is the major 110-kDa protein in GLUT4 vesicles from adipocytes. *J Biol Chem*. 1998; 273(6):3582-3587.(Biology)

Nielsen MS, Jacobsen C, Olivecrona G, Gliemann J, Petersen CM. Sortilin/neurotensin receptor-3 binds and mediates degradation of lipoprotein lipase. *J Biol Chem*. 1999; 274(13):8832-8836.(Biology)

Petersen CM, Nielsen MS, Nykjaer A. Molecular identification of a novel candidate sorting receptor purified from human brain by receptor-associated protein affinity chromatography. *J Biol Chem*. 1997; 272(6):3599-3605.(Biology)